Examiner Search Report

9/30/04
09/731,632

=> d his

(FILE 'HOME' ENTERED AT 10:48:03 ON 30 SEP 2004)

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, AQUALINE, ANABSTR, ANTE, AQUASCI, BIOBUSINESS, BIOCOMMERCE, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DISSABS, DDFB, DDFU, DGENE, ...' ENTERED AT 10:48:16 ON 30 SEP 2004

SEA CYCLOOXYGENASE OR COX

4273	FILE ADISCTI
108	FILE ADISINSIGHT
336	FILE ADISNEWS
907	FILE AGRICOLA
46	FILE AQUALINE
91	FILE ANABSTR
45	FILE ANTE
487	FILE AQUASCI
497	FILE BIOBUSINESS
33	FILE BIOCOMMERCE
264	FILE BIOENG
40750	FILE BIOSIS
201	FILE BIOTECHABS
201	FILE BIOTECHDS
6561	FILE BIOTECHNO
4278	FILE CABA
10632	FILE CANCERLIT
28655	FILE CAPLUS
128	FILE CEABA-VTB
60	FILE CEN
717	FILE CIN
546	FILE CONFSCI
12	FILE CROPB
123	FILE CROPU
2300	FILE DISSABS
99	FILE DDFB
9941	FILE DDFU
2189	FILE DGENE
99	FILE DRUGB
325	FILE DRUGMONOG2
255	FILE IMSDRUGNEWS
12058	FILE DRUGU
157	FILE IMSRESEARCH
742	FILE EMBAL
36343	FILE EMBASE
16125	FILE ESBIOBASE
1076	FILE FEDRIP
95	FILE FOMAD
279	FILE FROSTI
530	FILE FSTA
17034	FILE GENBANK
240	FILE HEALSAFE
2118	FILE IFIPAT
89	FILE IMSPRODUCT
3089	FILE JICST-EPLUS
28	FILE KOSMET
4509	FILE LIFESCI
58	FILE MEDICONF
39369	FILE MEDLINE
133	FILE NIOSHTIC
468	FILE NTIS
8	FILE NUTRACEUT
212	FILE OCEAN
19324	FILE PASCAL

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              781   FILE PHAR
              377   FILE PHARMAML
                6   FILE PHIC
             1124   FILE PHIN
            41169   FILE PROMT
             2333   FILE PROUSDDR
               31   FILE RDISCLOSURE
            36182   FILE SCISEARCH
               57   FILE SYNTHLINE
            22459   FILE TOXCENTER
            14790   FILE USPATFULL
             1064   FILE USPAT2
              245   FILE VETU
              119   FILE WATER
             3187   FILE WPIDS
               14   FILE WPIFV
             3187   FILE WPINDEX
L1               QUE CYCLOOXYGENASE OR COX
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     FILE 'PROMT, BIOSIS, MEDLINE, EMBASE, SCISEARCH, CAPLUS, TOXCENTER,
     PASCAL, ESBIOBASE, DRUGU, CANCERLIT' ENTERED AT 10:50:40 ON 30 SEP 2004
L2            524 S L1 AND OSTEOSARCOMA
L3              5 S L2 AND (143.98.2)
L4              2 DUP REM L3 (3 DUPLICATES REMOVED)
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=> d l4 ibib ab 1-2

L4 ANSWER 1 OF 2 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 97239482 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9085144
TITLE: Characterization of autocrine inducible prostaglandin H synthase-2 (PGHS-2) in human **osteosarcoma** cells.
AUTHOR: Wong E; DeLuca C; Boily C; Charleson S; Cromlish W; Denis D; Kargman S; Kennedy B P; Ouellet M; Skorey K; O'Neill G P; Vickers P J; Riendeau D
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Merck Frosst Centre for Therapeutic Research, Pointe-Claire-Dorval, Quebec, Canada.
SOURCE: Inflammation research : official journal of the European Histamine Research Society ... [et al.], (1997 Feb) 46 (2) 51-9.
Journal code: 9508160. ISSN: 1023-3830.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970620
Last Updated on STN: 19970620
Entered Medline: 19970612

AB The human **osteosarcoma 143.98.2** cell line was found to express high levels of prostaglandin synthase-2 (PGHS-2) without detectable levels of prostaglandin synthase-1 (PGHS-1) as measured by reverse transcriptase-polymerase chain reaction (RT-PCR) and immunoblot analysis. Maximal levels of PGHS-2 induction were attained when the cells were grown beyond confluence. The **osteosarcoma** cells also secrete IL-1 alpha, IL-1 beta and TNF alpha in the culture medium. PGHS-2 expression was inducible by the exogenous addition of these cytokines as well as conditioned media from auto-induced cultures and inhibitable by treatment with dexamethasone. In contrast, undifferentiated U937 cells selectively express PGHS-1 as analyzed by RT-PCR and Western blotting. The effects of non-steroidal anti-inflammatory drugs (NSAIDs) on the cellular PGE2 production mediated by each isoform of human PGHS were determined using **osteosarcoma** and undifferentiated U937 cells. When cells were preincubated with inhibitors to allow time-dependent inhibition prior to arachidonic acid stimulation, NS-398, CGP 28238, L-745,337, SC-58125 all behaved as potent (IC50 = 1-30 nM) and selective inhibitors of PGHS-2, in contrast to indomethacin, flurbiprofen or diclofenac which are potent inhibitors of enzymes. DuP-697 and sulindac sulfide were also potent inhibitors of PGHS-2 but both compounds inhibited cellular PGHS-1 activity at higher doses (IC50 = 0.2-0.4 microM). Time-dependent inhibition of PGE2 production in **osteosarcoma** cells was observed for indomethacin, diclofenac and etodolac. The synthesis of PGE2 by U937 cells was strongly dependent on exogenous arachidonic acid (100-fold stimulation) whereas confluent **osteosarcoma** cells also produced PGE2 without exogenous stimulus (7-fold stimulation by arachidonic acid). **Osteosarcoma** cells grown beyond confluence released more PGE2 from endogenous substrate than arachidonic acid stimulated undifferentiated U937 cells. These results indicate that **osteosarcoma** cells selectively express PGHS-2 with an autocrine regulation and effective utilization of endogenous arachidonic acid for PGE2 synthesis.

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 1995:339482 CAPLUS
DOCUMENT NUMBER: 122:105655
TITLE: Preparation of 2-substituted-3,4-di(aryl)thiophene **cyclooxygenase** inhibitors

INVENTOR(S): Gauthier, Jacques Yves; Leblanc, Yves; Prasit, Petpiboon
PATENT ASSIGNEE(S): Merck Frosst Canada Inc., Can.
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9426731	A1	19941124	WO 1994-CA264		19940511
W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TT, UA, US, UZ					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
CA 2161789	AA	19941124	CA 1994-2161789		19940511
AU 9467184	A1	19941212	AU 1994-67184		19940511
PRIORITY APPLN. INFO.:			US 1993-61354	A	19930513
			WO 1994-CA264	W	19940511

OTHER SOURCE(S): MARPAT 122:105655

AB The title compds. [I; R1 = H, halogen, CN, NO2, CF3, C1-6 alkyl; R2 = C3-6 alkyl, (un)substituted Ph, (un)substituted heteroaryl; R3 = SO2CH3, S(O)(NH)CH3, SONH2, SO2NH2; R4 = H, halogen, CO2H, CF3], useful as **cyclooxygenase** inhibitors, are prepared and I-containing formulations claimed. Thus, 3-(4-fluorophenyl)-4-(4-sulfamoylphenyl)thiophene was prepared and demonstrated 95% inhibition of PGE2 formation by **osteosarcoma** (**143.98.2**) cells at 100 nM.

1: Inflamm Res. 1997 Feb;46(2):51-9.

Characterization of autocrine inducible prostaglandin H synthase-2 (PGH 2) in human osteosarcoma cells.

Wong E, DeLuca C, Boily C, Charleson S, Cromlish W, Denis D, Kargman S, Kennedy BP, Ouellet M, Skorey K, O'Neill GP, Vickers PJ, Riendeau D.

Department of Biochemistry and Molecular Biology, Merck Frosst Centre for Therapeut Research, Pointe-Claire-Dorval, Quebec, Canada.

The human osteosarcoma 143.98.2 cell line was found to express high levels of prostaglandin synthase-2 (PGHS-2) without detectable levels of prostaglandin synthase-(PGHS-1) as measured by reverse transcriptase-polymerase chain reaction (RT-PCR) an immunoblot analysis. Maximal levels of PGHS-2 induction were attained when the cells were grown beyond confluence. The osteosarcoma cells also secrete IL-1 alpha, IL-1 bet and TNF alpha in the culture medium. PGHS-2 expression was inducible by the exogeno addition of these cytokines as well as conditioned media from auto-induced cultures and inhibitable by treatment with dexamethasone. In contrast, undifferentiated U937 cells selectively express PGHS-1 as analyzed by RT-PCR and Western blotting. The effects o non-steroidal anti-inflammatory drugs (NSAIDs) on the cellular PGE2 production media by each isoform of human PGHS were determined using osteosarcoma and undifferentia U937 cells. When cells were preincubated with inhibitors to allow time-dependent inhibition prior to arachidonic acid stimulation, NS-398, CGP 28238, L-745,337, SC-58125 all behaved as potent (IC50 = 1-30 nM) and selective inhibitors of PGHS-2, in contrast to indomethacin, flurbiprofen or diclofenac which are potent inhibitors of enzymes. DuP-697 and sulindac sulfide were also potent inhibitors of PGHS-2 but both compounds inhibited cellular PGHS-1 activity at higher doses (IC50 = 0.2-0.4 microM). Time-dependent inhibition of PGE2 production in osteosarcoma cells was observed for indomethacin, diclofenac and etodolac. The synthesis of PGE2 by U937 cells was strong dependent on exogenous arachidonic acid (100-fold stimulation) whereas confluent osteosarcoma cells also produced PGE2 without exogenous stimulus (7-fold stimulation arachidonic acid). Osteosarcoma cells grown beyond confluence released more PGE2 fro endogenous substrate than arachidonic acid stimulated undifferentiated U937 cells. Thes results indicate that osteosarcoma cells selectively express PGHS-2 with an autocrine regulation and effective utilization of endogenous arachidonic acid for PGE2 synthesis.

PMID: 9085144 [PubMed - indexed for MEDLINE]

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Search	Most Recent Queries	Time	Res
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#4	Search **#1 AND #2** Field: **Text Word,** Limits: **Publication Date from 1970 to 1992**	10:55:41	
#2	Search **osteosarcoma** Field: **Title,** Limits: **Publication Date from 1970 to 1992**	10:55:02	20
#1	Search **cyclooxygenase OR COX** Field: **Title,** Limits: **Publication Date from 1970 to 1992**	10:54:39	8

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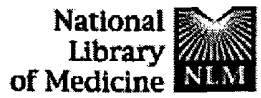

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